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08/203004

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/203,004	02/28/94	BERD D	1225/0C674

EXAMINER
UNGAR, S

ART UNIT	PAPER NUMBER
1642	36

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DATE MAILED: 4/28/99

This is a communication from the examiner in charge of your application.
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OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/15/99

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 43,44,47-76 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 43,44,47-76 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

1. The Election filed March 15, 1999 (Paper No. 35) in response to the Office Action of February 1, 1999 (Paper No. 33) is acknowledged and has been entered. Claims 43, 44, 47 and 49-76 are pending in the application and Claims 24-35 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 43, 44, 47 and 49-76 are currently under prosecution.

2. Applicant's election with traverse of the species of Melanoma and DNP in Paper No. 35 is acknowledged. The traversal is on the ground(s) that the no restriction of species was made in the grandparent application, Serial No. 07/520,649 filed May 8, 1990. The argument has been noted and found persuasive as drawn to the hapten species. However, the argument has not been found persuasive as drawn to the cancer type because a review of the cited application revealed that the reason that no election of species, drawn to types of cancers, was required was because no species were recited in the claims, further, the specification does not appear to be drawn to any type of cancer composition or methods of treatment, other than for melanoma. However, upon search of the elected species, it became clear that irradiated autologous cancer vaccines were well known in the art at the time the invention was made and that haptenization of tumor cell vaccines was well known, therefore there was no undue burden in the search of the species and the requirement is withdrawn. .

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. It is noted that a priority date of February 28, 1994 has been established for the instantly claimed application serial number 08/203,004 for all claims drawn to

breast, lung, colon, kidney or prostate tumors because the earlier filed applications do not disclose compositions comprising hapten modified tumor cell compositions or methods useful for the treatment of breast, lung, colon, kidney or prostate tumors. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of the priority date set forth above, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

New Grounds of Rejection

Double Patenting

5. Claims 47, 65-71, 73, 74, 76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No.5,290,551 . Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The patented claims are generic to the instant claims and render the species claims obvious as they have all the characteristics of a vaccine useful for the treatment of a malignant tumor, melanoma, in a human patient comprising irradiated autologous melanoma cell conjugated to a hapten selected from the group including DNP mixed with an immunological adjuvant wherein said immunological adjuvant is BCG and a method of treating melanoma comprising administering cyclophosphamide followed by administration of a therapeutically effective amount of the claimed vaccine. The limitations recited drawn to eliciting an inflammatory immune response against a delayed hypersensitivity response against the tumor, activated T lymphocytes that infiltrate the tumor wherein the T lymphocytes are predominantly CD8+CD4- are inherent properties of the method since the

population that is treated and the method steps recited in US Patent No. No.5,290,551 are the same as those of the instant claims. Thus, because the method of the patent comprises the same method steps as claimed in the instant invention, with the same population, the claimed method is made obvious because the method will inherently lead to eliciting an inflammatory immune response against a delayed hypersensitivity response against the tumor, activated T lymphocytes that infiltrate the tumor wherein the T lymphocytes are predominantly CD8+CD4-. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Further, the recitation of repetition of administration of the vaccine at least six times at spaced apart intervals in claim 47 does not render the claims unobvious because immunization schedules requiring administration of antigen at least six times at spaced intervals are conventional in the immunostimulation arts as demonstrated by the teaching in US Patent No. 5,702,704 (col 20, lines 12-26), No. 5,626,843 (col. 4, lines 28-38), No. 5,008,183 col 5 lines 48-54), No. 4,232,001 (col 5, lines 25-27) which all teach immunization with at least six booster injections of antigen. Although the teaching is drawn to the antibody art, it is well known that T cells must be stimulated in order to produce the detected antibodies.

Applicant's argument in Paper No. 32 drawn to claims 47 and 76 are relevant to the instant rejection. Applicant argues that claim 47 calls for treating cancer by administering human tumor cells by repeating administration at least 6 times and claim 76 claims that administration elicits predominantly CD4-CD8+ T lymphocytes and that these claims are not suggested by the claims of the '551 patent. The argument has been noted but has not been found persuasive for the reasons stated

above, that is that the 6 time repetition is conventional in the immunostimulation art and that the CD4-CD8+ limitation is an inherent property of the method.

Claim Rejections - 35 USC § 112

6. Claims 44, 47, 56-62, 65-72 and 75-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a malignant tumor in a human patient comprising administering the composition of claim 43 and BCG, does not reasonably provide enablement for treatment a malignant tumor in a human patient without administering an BCG in combination with the claimed composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to treatment of malignant tumors with a composition comprising a hapten conjugated to a tumor cell. The specification teaches a melanoma vaccine administered with BCG and describes immune responses to the melanoma vaccine administered with BCG (page 19-43) and specifically teaches in the sentence bridging pages 27-28 that "all vaccines were DNP-conjugated and mixed with BCG". It appears that the inclusion of the adjuvant may be a critical step since Livingstone et al (of record) disclosed that in a melanoma vaccine using the GM2 ganglioside, antibody responses were not induced unless BCG was added to the purified GM2 vaccine (p. 2913, paragraph bridging columns 1 and 2). Livingstone et al also state that "adjuvants ..... were important factors in the mouse studies and results of the present human trials indicate their importance in melanoma patients". Hoover et al, of record, also used BCG as an adjuvant in a colorectal cancer vaccine and states that the correct amount of the appropriate adjuvant was a

critical condition of the success of the immunotherapy (p. 1242, col 1, para 2). Based on the teachings above and in the specification one of skill in the art would not expect that the claimed method would be effective in treating cancer with DNP-conjugated vaccines without specifically including BCG as demonstrated in the specification. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention

7. Claim 73 is rejected under 35 USC 112, fourth paragraph because it does not further limit claim 47 from which it depends.

Claim Rejections - 35 USC § 102

8. Claim 76 is rejected under 35 U.S.C. § 102(a) as being anticipated by Murphy et al, of record.

The claim is drawn to a method of treating a malignant tumor in a patient comprising administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection therein, said administration eliciting T lymphocytes that infiltrate the tumor and that are predominantly CD8+CD4-.

Murphy et al teach a method for treating melanoma comprising administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells. Although the reference does not disclose, the elicitation of T lymphocytes that infiltrate the tumor and are predominantly CD8+CD4-, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering to the patient a composition comprising a therapeutically

effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection to the same population, thus the claimed method is anticipated because the method will inherently lead to eliciting T lymphocytes that infiltrate the tumor and that are predominantly CD8+CD4-. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant's arguments in Paper No. 32 drawn to the rejection of claim 76 under 35 USC 102(a) are relevant to the instant rejection. Applicant argues that new claim 76 calls for a method of treating cancer by administering hapten-conjugated human tumor cells wherein said administering elicits predominantly CD4-CD8+ T lymphocytes and the Murphy et al paper does not disclose this limitation. The argument has been noted but has not been found persuasive for the reasons disclosed above, that is that the elicitation of specific T lymphocytes that infiltrate the tumor is an inherent property of the method.

9. Claim 76 is rejected under 35 U.S.C. § 102(b) as being anticipated by Berd et al., Proc. AACR, 1989, 30:382, of record.

The claim is drawn to a method of treating a malignant tumor in a patient comprising administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection therein, said administration eliciting T lymphocytes that infiltrate the tumor and that are predominantly CD8+CD4-.

Berd et al teach a method for treating melanoma comprising administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells. Although the reference does not disclose, the elicitation of the T lymphocytes that infiltrate the tumor and are predominantly CD8+CD4-, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection, to the same population, thus the claimed method is anticipated because the method will inherently lead to eliciting T lymphocytes that infiltrate the tumor and that are predominantly CD8+CD4-. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant's arguments in Paper No. 32 drawn to the rejection of claim 76 under 35 USC 102(b) are relevant to the instant rejection. Applicant argues that new claim 76 calls for a method of treating cancer by administering hapten-conjugated human tumor cells wherein said administering elicits predominantly CD4-CD8+ T lymphocytes and the Berd et al does not disclose this limitation. The argument has been noted but has not been found persuasive for the reasons disclosed above, that is that the elicitation of specific T lymphocytes that infiltrate the tumor is an inherent property of the method.

Claim Rejections - 35 USC § 103

10. Claims 47, 65-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Murphy et al, of record draw to claim 76 in view of US Patent No. 5,702,704,

No. 5,626,843, No. 5,008,183 or No. 4,232,001 and Berd et al., Proc. AACR, 1989, 30:382, of record and Geczy et al, of record.

The claims are drawn to a method of treating a malignant tumor in a patient comprising administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection therein, said composition eliciting at least one of the following upon administration to said patient with an adjuvant: an inflammatory immune response against the tumor; a delayed-type hypersensitivity response against the tumor; and activated T lymphocytes that infiltrate the tumor and repeating said administration at least six times at spaced apart intervals, wherein said tumor cells are selected from a group including melanoma, wherein the treating is useful for treatment of cancer selected from a group including melanoma, wherein said hapten is selected from the group including DNP, wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition, wherein the dose is about 300 mg/M^2, wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide wherein the composition comprises an adjuvant, BCG, wherein the life of the patient is prolonged, wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

Murphy et al teach as set forth above and further teach a method for treating melanoma comprising sensitizing with DNCB, administering a therapeutically effective amount of cyclophosphamide and administering a therapeutically effective

amount of autologous, irradiated DNP-conjugated melanoma cells mixed with the adjuvant BCG. Murphy et al teach as set forth above but do not teach a method wherein the vaccine is boosted at least six times at spaced intervals, the administration of 300 mg/M^2 of cyclophosphamide, prior sensitization with 1-fluoro-2,4-nitrobenzene or eliciting at least one of the following upon administration to said patient with an adjuvant: an inflammatory immune response against the tumor; a delayed-type hypersensitivity response against the tumor; and activated T lymphocytes that infiltrate the tumor or wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-, wherein the life of the patient is prolonged.

US Patent No. 5,702,704 (col 20, lines 12-26), No. 5,626,843 (col. 4, lines 28-38), No. 5,008,183 col 5 lines 48-54), No. 4,232,001 (col 5, lines 25-27) all teach conventional immunization schedules wherein antigen administration is repeated at least six times at spaced intervals.

Berd et al teach a successful method of treating melanoma wherein a therapeutically effective amount of cyclophosphamide, 300 mg/M^2 of cyclophosphamide, is administered prior to autologous, irradiated, DNP-conjugated melanoma cells.

Geczy et al teach that halogenated dinitrobenzenes such as 1-chloro- and 1-fluoro-2,4-dinitrobenzene are commonly used to elicit delayed hypersensitivity (p. 189, para 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Murphy et al and the cited patents because it is clearly conventional to repeat antigen administration at

least six times at spaced intervals. Although the teaching is drawn to the antibody art, it is well known that T lymphocytes must be stimulated in order to produce the detected antibodies. One of ordinary skill in the art at the time would have expected to successfully use the method with the conventional immunization schedule. Further, although the limitations drawn to an inflammatory immune response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4- are not recited in the reference, the method of the prior art comprises the same method steps as claimed in the instant invention, to treat the same population, thus the claimed method is anticipated because the method will inherently lead to an inflammatory immune response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a dose of 300 mg/M^2 of cyclophosphamide in the method of Murphy et al because Berd et al teach that the dose is therapeutically effective in a method which uses the same haptenized melanoma cells with the same population of patients. One of ordinary skill in the art would have expected to successfully use the method of Murphy with a dosage of 300 mg/M^2 of cyclophosphamide because Berd et al demonstrated the successful use of the method. Finally, it would have been *prima facie* obvious to substitute DNFB for the DNCB of Murphy et al because Geczy et

al teach that halogenated dinitrobenzenes such a 1-chloro- and 1-fluoro-2,4, dinitrobenzenes are commonly used to elicit delayed hypersensitivity and are clearly closely related haptenic molecules which function to produce the same effects and are therefore functionally equivalent. Finally, as drawn to prolonged survival, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the method of the prior art does not result in prolonged survival of the patient and is functionally different than the method taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Applicant's arguments drawn to the rejection of claims 47, 65-71, 73 and 74 in Paper No. 32 are relevant to the instant rejection.

Applicant argues that claims 47, 65-71, 73 and 74 are not anticipated by Murphy et al because claims 65-71, 73 and 74 depend from claim 47. The argument has been noted but has not been found persuasive for the reasons disclosed above.

11. Claims 47, 65-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al., Proc. AACR, 1989, 30:382, of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001 and Geczy et al, of record.

The claims are drawn to a method of treating a malignant tumor in a patient comprising administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection therein, said composition eliciting at least one of the following upon administration to said patient with an adjuvant: an inflammatory immune response against the tumor; a delayed-type hypersensitivity response against the tumor; and activated T lymphocytes that infiltrate the tumor and repeating said administration at least six times at spaced apart intervals, wherein said tumor cells are selected from a group including melanoma, wherein the treating is useful for treatment of cancer selected from a group including melanoma, wherein said hapten is selected from the group including DNP, wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition, wherein the dose is about 300 mg/M^2, wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide wherein the composition comprises an adjuvant, BGC, wherein the administration prolongs survival of said patient wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

Berd et al teach a method for treating melanoma comprising sensitizing with DNCB, administering 300 mg/M^2 of cyclophosphamide prior to administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells mixed with the adjuvant BCG wherein the patients are sensitized

with DNCB prior to cyclophosphamide administration. Berd et al teach as set forth but do not teach a method wherein the vaccine is boosted at least six times at spaced intervals or eliciting at least one of the following upon administration to said patient with an adjuvant: an inflammatory immune response against the tumor; a delayed-type hypersensitivity response against the tumor; and activated T lymphocytes that infiltrate the tumor or wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4- or that the administration prolongs survival of the patient.

US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 and No. 4,232,001 and Geczy et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Berd et al and the cited patents because it is clearly conventional to repeat antigen administration at least six times at spaced intervals. Although the teaching is drawn to the antibody art, it is well known that T lymphocytes must be stimulated in order to produce the detected antibodies. One of ordinary skill in the art at the time would have expected to successfully use the method with the conventional immunization schedule. Further, although the limitations drawn to an inflammatory immune response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor, wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-. are not recited in the reference, the method of the prior art comprises the same method steps as claimed in the instant invention, and the same population, thus the claimed method is anticipated because the method will

inherently lead to an inflammatory immune response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor wherein the administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). It would have been *prima facie* obvious to substitute DNFB for the DNCB of Berd et al because Geczy et al teach that halogenated dinitrobenzenes such a 1-chloro- and 1-fluoro-2,4, dinitrobenzenes are commonly used to elicit delayed hypersensitivity and are clearly closely related haptenic molecules which function to produce the same effects and are therefore functionally equivalent. Finally, as drawn to prolonged survival, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the method of the prior art does not result in prolonged survival of the patient and is functionally different than the method taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

12. Claims 43, 44, 47 and 49-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al., Proc. AACR, 1989, 30:382, of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001 and Geczy

et al, of record, as applied to claims 47, 65-76 and further in view of Wiseman et al (Western J. Med., 1989, 151:283-288).

The claims are drawn to a composition comprising human tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of a patient for whom treatment with the composition is intended, are autologous to said patient, have been rendered incapable of growing in the body of a human upon injection therein said composition eliciting an inflammatory immune response against the tumor wherein the tumor is not melanoma, a method for treating a malignant tumor in a human patient comprising administering said composition to the patient wherein said composition elicits, following administration of said composition with an adjuvant, BCG at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor, wherein the tumor cells are selected from lung, colon and kidney, wherein said hapten is selected from the group including DNP and TNP, wherein the composition further comprises a carrier which is a saline solution or culture medium, wherein the method is useful for the treatment of lung cancer, colon cancer, or kidney cancer, wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide, 300 mg/M^2, further comprising sensitizing the patient to a therapeutically effective amount of 1-fluoro-2,4, dinitrobenzene prior to administering cyclophosphamide, wherein said administration prolongs survival of the patient, wherein said administration elicits T lymphocytes that infiltrate the tumor said lymphocytes being predominantly CD8+CD4.

Berd et al (1989) record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001, and Geczy et al teach as set forth above but the combined references do not teach a composition or method of treatment wherein the tumor cells are kidney, colon, lung or wherein the cancer treated is kidney cancer, colon cancer or lung cancer.

Wiseman et al teaches compositions comprising autologous irradiated melanoma cancer cells, lung cancer cells, colon cancer cells and kidney cancer cells which are administered to treat patients with melanoma, lung cancer, colon cancer, and kidney cancer (Table 3, page 285), respectively wherein the patients were pretreated with 300 mg/M^2 cyclophosphamide (see abstract - Drug Table) wherein the patients showed increased immunological responses to the cancer (see abstract) wherein patients with, lung cancer, colon cancer, and kidney cancer all showed prolonged survival (Table 3, page 285).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the lung cancer cells, colon cancer cells or kidney cancer cells of Wiseman et al in the method of Berd et al because each of these cell types had been demonstrated to be immunogenic and to elicit responses in the respective cancer patients and because Berd et al teaches that haptenizing cancer cells increases the efficiency of the immunizing process. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the tumor cells of Wiseman et al into the method of Berd et al because Wiseman et al teach that their method prolongs survival in some cases and Berd et al teach that their method increases efficiency of the immunization process, thus increased efficiency would be expected to result in increased treatment

efficacy. Further, as drawn to claims 54-55, it is clearly obvious to include a saline carrier in a composition which is prepared for *in vivo* administration because it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960). Finally, as drawn to the limitations including, eliciting an inflammatory immune response against the tumor, at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T, elicits T lymphocytes that infiltrate the tumor said lymphocytes being predominantly CD8+CD4, the claimed compositions and methods of treatment appear to be the same or similar to those of the combined references absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product or methods with the product or methods of the combined prior art in order to establish that the product or methods of the combined prior art does not possess the same material structural and functional characteristics of the claimed product or methods. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and methods are functionally different than those taught by the combined prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

13. Claims 43, 44, 47 and 49-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al. (1989) of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001, Geczy et al, of record, as applied

to claims 43, 44, 47 and 49-76 and further in view of Berd et al (Proc. Am. Soc. Clin. Oncol., 1983, Vol 2:56)

The claims are drawn to a composition comprising human tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of a patient for whom treatment with the composition is intended, are autologous to said patient, have been rendered incapable of growing in the body of a human upon injection therein said composition eliciting an inflammatory immune response against the tumor wherein the tumor is not melanoma, a method for treating a malignant tumor in a human patient comprising administering said composition to the patient wherein said composition elicits, following administration of said composition with an adjuvant, BCG at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor, wherein the tumor cells are selected from the group including breast, wherein said hapten is selected from the group including DNP and TNP, wherein the composition further comprises a carrier which is a saline solution or culture medium, wherein the method is useful for the treatment of breast cancer wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide, 300 mg/M^2, further comprising sensitizing the patient to a therapeutically effective amount of 1-fluoro-2,4, dinitrobenzene prior to administering cyclophosphamide, wherein said administration elicits T lymphocytes that infiltrate the tumor said lymphocytes being predominantly CD8+CD4-.

Berd et al., (1989) of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001, Geczy et al, of record, as applied to

claims 43, 44, 47 and 49-76 teach as set forth above but the combined references do not teach a composition or method of treatment wherein the tumor cells are breast or wherein the cancer treated is breast cancer or wherein the life of the patient is prolonged.

Berd et al (1983) teach a composition and a method for the treatment of breast carcinoma comprising administration of autologous tumor cell/BCG preceded by cyclophosphamide which administration resulted in delayed-type hypersensitivity in 5 patients.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the breast cancer cells of Berd et al (1983) in the method of Berd et al (1989) because this cell type had been demonstrated to be immunogenic and to elicit responses in the breast cancer patients and one of ordinary skill in the art would have been motivated to substitute the breast cancer cells of Berd et al (1983) in the method of Berd et al (1989) because Berd et al teaches that haptenizing cancer cells increases the efficiency of the immunizing process, thus increased efficiency would be expected to result in increased treatment efficacy. Further, as drawn to claims 54-55, it is clearly obvious to include a saline carrier in a composition which is prepared for *in vivo* administration because it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960). Finally, as drawn to the limitations including, eliciting an inflammatory immune response against the tumor, at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T, elicits T lymphocytes

that infiltrate the tumor said lymphocytes being predominantly CD8+CD4 and administration leading to prolonged survival of the patient, the claimed compositions and methods of treatment appear to be the same or similar to those of the combined references absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product or methods with the product or methods of the combined prior art in order to establish that the product or methods of the combined prior art does not possess the same material structural and functional characteristics of the claimed product or methods. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and methods are functionally different than those taught by the combined prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int. Finally although the reference does not specifically teach irradiation of the tumor cells prior to administration, it is clear that it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to treat the cells to prevent their growth in a body prior to administration, in order to prevent exogenously derived cancer in the patient.

14. Claims 43, 44, 47 and 49-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al., Proc. AACR, 1989, 30:382, of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001, Geczy et al, of record, as applied to claims 43, 44, 47 and 49-76 and further in view of Sanda et al (J. Cellular Biochem. Suppl. No. 17, Part D, p. 120) and Moody et al (J. Urol., 1991, 145:293A).

The claims are drawn to a composition comprising human tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of a patient for whom treatment with the composition is intended, are autologous to said patient, have been rendered incapable of growing in the body of a human upon injection therein said composition eliciting an inflammatory immune response against the tumor wherein the tumor is not melanoma, a method for treating a malignant tumor in a human patient comprising administering said composition to the patient wherein said composition elicits, following administration of said composition with an adjuvant, BCG at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor, wherein the tumor cells are prostate, wherein said hapten is selected from the group including DNP and TNP, wherein the composition further comprises a carrier which is a saline solution or culture medium, wherein the method is useful for the treatment prostate cancer, wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide, 300 mg/M^2, further comprising sensitizing the patient to a therapeutically effective amount of 1-fluoro-2,4, dinitrobenzene prior to administering cyclophosphamide, wherein the life of the patient is prolonged, wherein said administration elicits T lymphocytes that infiltrate the tumor said lymphocytes being predominantly CD8+CD4-.

Berd et al. (1989), of record, in view of US Patent No. 5,702,704, No. 5,626,843, No. 5,008,183 or No. 4,232,001, Geczy et al, of record, as applied to claims 43, 44, 47 and 49-76 teach as set forth above but the combined references do not teach a composition or method of treatment wherein the tumor cells are prostate

or wherein the cancer treated is prostate cancer or wherein the life of the patient is prolonged.

Moody et al (J. Urol., 1991, 145:293A) teach that lymphokine-transfected prostate cells generate an anti-tumor effect *in vivo* against rapidly growing rat prostate carcinoma induced by autologous, cells that were not transfected.

Sandra et al addressed the feasibility of gene therapy for human prostate cancer by demonstrating that retroviral vector MFG allows high efficiency transduction of human prostate cancer cells which was demonstrated in primary culture prostate cancer cells from 7 consecutive patients which demonstrates the feasibility of using MFG in genetic therapy for prostate cancer (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the prostate cancer cells of Sandra et al, transfected with lymphokine in the method of Moody et al for the melanoma cells in the method of Berd et al because Moody et al have demonstrated in an appropriate animal model that lymphokine-transfected prostate cells generate an anti-tumor effect *in vivo* against rapidly growing prostate carcinoma and because Sandra et al have demonstrated the feasibility of gene therapy for human prostate cancer by demonstrating the successful transfection of human prostate cancer cells with retroviral vector MFG. One of ordinary skill in the art would have been motivated to substitute the prostate cancer cells of Sandra et al, transfected with lymphokine in the method of Moody et al for the melanoma cells in the method of Berd et al because autologous anti-cancer cell vaccination was known to those of ordinary skill in the art and because Berd et al teach that the method that

haptenizing cancer cells increases the efficiency of the immunizing process, thus increased efficiency would be expected to result in increased treatment efficacy. Further, as drawn to claims 54-55, it is clearly obvious to include a saline carrier in a composition which is prepared for *in vivo* administration because it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960). Finally, as drawn to the limitations including, eliciting an inflammatory immune response against the tumor, at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T, elicits T lymphocytes that infiltrate the tumor said lymphocytes being predominantly CD8+CD4 and administration leading to prolonged survival of the patient, the claimed compositions and methods of treatment appear to be the same or similar to those of the combined references absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product or methods with the product or methods of the combined prior art in order to establish that the product or methods of the combined prior art does not possess the same material structural and functional characteristics of the claimed product or methods. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and methods are functionally different than those taught by the combined prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int. Although neither the Moody et al or Sandra et al reference specifically teaches irradiation of the tumor cells prior to administration, it is clear that it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to treat the cells to

prevent their growth in a body prior to administration, in order to prevent exogenously derived cancer in the patient.

15. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of February 28, 1994 for the instantly claimed application serial number 08/203.004, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar

SUSAN UNGAR
PATENT EXAMINER

April 26, 1999